Kimura et al. does not teach the usefulness of these compounds to treat cachexia or disorders resulting from tumors, Strelkov et al. is relied on to teach that the inhibition of prostaglandin production (by Naproxen) counters tumor related cachexia or muscle wasting and other deleterious side effects of tumors.

The Examiner takes the position that the teaching in Strelkov provides a reasonable expectation of success (for all prostaglandin inhibitors). The Examiner relies on tables showing weight gain in the presence of Naproxen (a prostaglandin inhibitor) as evidence of a teaching of nexus between the inhibition of prostaglandin and decrease in muscle wasting.

The art in fact fails to teach how to use prostaglandin inhibitors for the claimed method and only hypothesizes the inhibition of prostaglandin possibility that they may be useful. At best this is an "obvious to try" disclosure and not one which renders the present claimed invention obvious (e.g. page C267, column 1, third paragraph "The results of this study suggest that PGE_2 production by a tumor may participate in the progression of cachexia in the host.".

In the AMENDMENT filed February 22, 2002, applicants noted that at the time this invention was made, the most remarkable COX-2 inhibitors were Compound (III) which is now marketed by Pfizer under the name "Celebrex", and Compound (IV) which is now

marketed by Merck under the name "Vioxx". Therefore, even if one were convinced by the prior art that the inhibition of prostaglandin as described in Strelkov was useful, one would expect the best effect from these two compounds thereby establishing an expectation level of activity for a person skilled in the art. However, as shown in the test data in the present specification (Tables 3, 4 and 5) claimed Compound No. 2-78 and Compound No. 1-94 possess unexpectedly superior activity as anti-cachexia agents. Referring to the data in Tables 3, 4 and 5, note is made especially at the "dose: 1 mg/kg" of the reported "weight gain" for each compound.

The Examiner dismissed these results as not describing testing between compounds as claimed and the prior art even though the tested compounds appear to be the best compounds from the point of view of expected activity. To respond to the issues raised by the Examiner, applicants have had further testing accomplished and this testing is shown in the enclosed DECLARATION.

The testing in the enclosed DECLARATION is against the prior art compound "Naproxen." This was selected because Naproxen was the prostaglandin inhibitor disclosed and used by Strelkov. In fact, Naproxen is the only prostaglandin inhibitor mentioned in Strelkov. Therefore, it is submitted that comparison with

Naproxen meets the objection to the test data which was raised by the Examiner.

Considering the enclosed and especially the testing summarized in the Table of the DECLARATION, as can be seen from the results, the two compounds which are required by the claims in the present application have very much higher activity than Naproxen. Thus, for example, a dosage of 10 mg/kg of Naproxen shows about 1/10 of the body weight gain as does a dose of 1 mg/kg of either of the two compounds required by the present invention claims. Also for body weight recovery the compounds required by the present invention claims were significantly higher in recovery rate.

Such high activity could not have been expected based on the prior art.

It is submitted that the prior art, in combination, at best provides an obvious-to-try situation without an explanation as to how to use the compounds or a clear expectation of success. However, even if one could make a *prima facie* obviousness case, one would not expect the surprisingly superior results which are obtained with the present invention as compared with the compounds disclosed in the cited art.

In view of the above, withdrawal of the rejections and allowance of the application are respectfully requested.

Respectfully submitted,

Frishauf, Holtz, Goodman,
& Chick, P.C.
767 Third Ave., 25th Floor
New York, NY 10017-2023
Tel. No. (212) 319-4900
Fax No.: (212) 319-5101
MJC/ld

MARSHALL J. CHICK
Reg. No. 26,853

Enc. Facsimile Executed DECLARATION UNDER 37 CFR 1.132 of Dr. Shinichi KURAKATA dated September 10, 2002